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Rat Heart Structural and Functional Characteristics and Gas Exchange Parameters after Experimental Myocardial Infarction

E. V. Baidyuk[a, *], G. A. Sakuta[a], L. P. Kislyakova[b], Yu. Ya. Kislyakov[b], S. V. Okovityi[c], and B. N. Kudryavtsev[a]

[a] *Institute of Cytology, Russian Academy of Sciences, St. Petersburg, Russia*
[b] *St. Petersburg State University of Analytical Instrumentation, St. Petersburg, Russia*
[c] *Chemical Pharmaceutical Academy, St. Petersburg, Russia*
**e-mail address: katya_bay@mail.ru*

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Abstract—Structural and functional changes in the heart and the parameters of gas exchange in rats were analyzed 6 months after initiation of myocardial infarction. With the aid of echocardiography, an increase was revealed of the terminal systolic and terminal diastolic sizes of the left heart ventricle in rats with chronic heart failure as compared with control by 78 and 30%, respectively. The volumes of the left ventricle in the systole and diastole were even greater—by five and two times, respectively. Dilation of the left ventricle cavity was accompanied by a thinning of the interventricular septum. As a result of structural changes of the left ventricle, its ability to function was significantly degraded. The shortening fraction in chronic heart failure decreased by 60%, while the output fraction decreased by 52%, compared with the corresponding parameters in control rats. Measurement of gas exchange showed that oxygen consumption in rats with chronic heart failure increased by almost 30%, while production of carbon dioxide by more than 40%. The respiration coefficient in rats with chronic heart failure amounted to 0.85, which indicates a significant increase of contribution of carbohydrates as energy substrates in metabolism of myocardium.

Keywords: myocardial infarction, chronic heart failure, echocardiography, respiratory coefficient

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INTRODUCTION

Cardiovascular diseases are very common pathologies in human beings. The main diseases of the circulatory system are hypertonic disease and atherosclerosis, as well as the stenocardia and myocardial infarction (MI) that are associated with them. Ischemia in the acute MI period can lead to the death of up to 40% of heart muscle cells (Saraste et al., 1999; Abdel-Latif et al., 2007; Buja and Vela, 2008). After several weeks of inflammation and reparative processes in the myocardium, these cells are mainly replaced by scar tissue. The loss of functioning myocardium can lead to the development of acute heart failure. However, even with a rather small zone of necrosis in the heart tissue, the load on the remaining cardiomyocytes increases, bringing about chronic heart failure (CHF) (Okonko et al., 2008). Adaptive changes of structure of myocardium and of geometry of the left ventricle (LV), which are often referred to as "remodeling," allow the systolic volume to be maintained at the normal level and, thereby, compensate for the decrease in the ejection fraction (EF) (Nechesova et al., 2008). The compensated tonogenic dilation (the dilation caused by an increase of the intracavity pressure) is increased by widening of the heart chambers due to dystrophic changes of myocardium—that is, myogenic heart dilation (Lang, 1958; Mareev et al., 2013). When the LV is damaged, overfilling with blood under elevated pressure occurs mainly in the left atrium and in the pulmonary circulation by producing congestion in lungs, which leads to their function being hindered (Friedman et al., 1976; Berger et al., 2004). The most important consequence of these disturbances of hemodynamics during heart failure is a decrease of supply of tissues with oxygen. Oxygen is used in tissues more intensely than normally during heart failure: instead of 30%, up to 60–70% is absorbed (Lang, 1958). Since the supply of tissues with oxygen remains insufficient, their biochemical processes become disturbed, lactic acid is accumulated in blood, and hidden or compensated acidosis develops. When it is difficult for the lungs to expel carbon dioxide, decompensated acidosis develops. These disturbances of

Abbreviations: MI—myocardial infarction, TDS—terminal diastolic size of LV, TSS—terminal systolic size of LV, LV—left ventricle, LA—left atrium, IVS—interventricular septum, CO—cardiac output, SV—systolic volume, EF—ejection fraction, SF—shortening fraction, CHF—chronic heart failure, HR—heart contraction rate, EchoCG—echocardiographic study.

carbohydrate metabolism bring about avalanche-like deterioration of the basic metabolism (Friedman et al., 1976).

The goal of the present work consisted in studying delayed post-MI disturbances of function of the rat heart and respiratory system—specifically, of morphological heart parameters with the aid of echocardiography—as well as in evaluation of some characteristics of respiration (rate of oxygen consumption and of carbon dioxide release).

MATERIALS AND METHODS

Studies were carried out on 22 white male Wistar rats the age of which was 4 months at the beginning of the experiment, while their body mass was 250–300 g. At the beginning of the experiment, the animals were subdivided into three groups: (1) control rats (C) not subjected to anything during the experiment (12 rats), (2) sham-operated (SO) rats (4 rats), and (3) rats with CHF that had developed as a result of experimental MI (6 rats).

MI in rats was produced by the *method of permanent ligation of the left coronary artery* (Baidyuk et al., 2012).

The volume of scar tissue in rat heart 6 months after coronary occlusion was found by the method of spatial reconstruction using serial heart LV histological sections stained with picrosirius red (50–60 LV sections 6 μm in thickness). In each section, with the aid of a PhotoM image analyzer, we determined the portion occupied by scar tissue.

Echocardiographic (EchoCG) study of the rat heart was performed in normal circumstances and in CHF prior to determination of gas exchange. Before the EchoCG study was carried out, the animals were subjected to general anesthesia by intraperitoneal introduction of thiopental at a dose of 60 mg/kg. An ultrasound Acuson Sequoia 512 system (Siemens-Acuson, Germany) with a linear sensor (frequency 8 MHz) was used to perform the EchoCG study. The studies were done in accordance with standard procedures in the regime of monomeric (M regime) and bimeric (B regime) scanning. The study was carried out at the parasternal long and short axes (at the level of cusps of mitral valve, at the level of papillary muscles, and at the level of cusps of the aortal valve), as well as in the four-chamber position.

The EchoCG parameters were measured in five cardiac cycles by obtaining mean values. In the systole, the measurements were performed at the moment corresponding to the end of peak T in the simultaneously recorded ECG, while in the diastole they were performed at the period of appearance of peak Q in the ECG. In the M regime, the diameter of the aorta at the root (Ao), the anterior–posterior LV size (LV, a-p), the anterior–posterior left atrium size (LA, a-p), the terminal diastolic and LV sizes (TDS, TSS), the thickness of the interventricular septum (Tivs), and the thickness of the posterior wall (Tpw) were measured. In the B regime, the transverse (t) and vertical (v) sizes of the left and right ventricles and of the left and right atria (LVt, LVv, RVt, RVv, LAt, LAv, RAt, RAv) were measured. In addition, the parameters of LV contractivity—the shortening fraction (SF = TDS – TSS/TDS × 100; %) with calculation of TDV (the terminal diastolic volume of LV) and TSV (terminal systolic volume of LV)—were calculated according to Teichholz et al. (1976).

Studies of gas exchange in rats in normal conditions and in CHF were carried out with the use of a specially designed experimental facility—a complex including a metabolic chamber for a rat and a computerized multiparametric analyzer of O_2 consumption and CO_2 release including a modification of an earlier developed model of the Ergo-test (University of Analytical Instrumentation of the Russian Academy of Sciences, Russia). The animal was placed into a closed metabolic chamber, and the rate of oxygen consumption (V_{O_2}, V_2 mL/min) and release of carbon dioxide (V_{CO_2}, V_{CO_2} mL/min) by the rat were determined using methods of amperometry (measurement of pO_2 in gaseous media) and absorptional infrared spectroscopy in the mid-infrared range (measurement of pCO_2 in gaseous media) under conditions of free behavior (Maslova et al., 2009).

The data in the tables are presented as the mean and its error ($X \pm Sx$). The significance of the differences between values was determined by using Student's t criterion at a significance level of $p < 0.05$.

RESULTS AND DISCUSSION

Over a lifetime, the heart experiences huge loads accompanied by wear and tear and various forms of damage to cardiomyocytes, which can end in the deaths of these cells. Harmful effects, as well as hereditary predisposition, lead to the development of various pathologies of the heart. Heart failure is the final stage of all heart diseases and the main cause of deaths among human beings (Kharchenko, 2005; Mareev et al., 2013).

CHF is a pathological state in which the cardiovascular system is unable to provide an organism with sufficient oxygen, first during physical activity and then at rest. Its main clinical manifestations are tachycardia, dyspnea, fatigue and a decrease in physical activity, cyanosis, edemas, enlargement of the liver, etc. (Damman et al., 2007; Felker et al., 2007; Alvarez and Mukherrjee, 2011).

Ligation of the left coronary artery in rats leads to subsequent changes in the myocardium similar to those that develop in human beings in infarction and subsequent CHF (Rumyantsev, 1978; Kruglyakov et al., 2004). The data presented in Table 1 indicate heart hypertrophy. In spite of the fact that the absolute

Table 1. Mass of body, heart, and LV of rats in various experimental groups

Groups of rats	M_b, g	M_h, g	M_{lv}, g	M_h/M_b, %	M_{lv}/M_b, %
C	503 ± 20	1.528 ± 0.065	0.723 ± 0.035	0.304 ± 0.003	0.144 ± 0.003
SO	467 ± 50	1.302 ± 0.103	0.592 ± 0.048	0.282 ± 0.009	0.128 ± 0.004
CHF	442 ± 17	1.538 ± 0.053	0.791 ± 0.030	0.350 ± 0.018[a]	0.180 ± 0.01[a]

M_b, M_h, and M_{lv} are mass of body, heart, and LV, respectively. Here and in Tables 2 and 3, C is the control group of animals, while SO is Sham-operated rats.
([a]) Difference from control, $p < 0.05$. Mean values and their errors are presented.

Table 2. Echocardiographic parameters of rat hearts in various experimental groups

Parameter	C	SO	HCF	Degree of change of parameters of SO as compared with C, %	Degree of change of parameters of HCF as compared with C, %	Degree of change of parameters of HCF as compared with SO, %
Ao (root), cm	0.410 ± 0.010	0.398 ± 0.013	0.390 ± 0.016	–	–	–
LA (a-p)	0.372 ± 0.013	0.340 ± 0.027	0.382 ± 0.035	–	–	–
RV, cm	0.340 ± 0.013	0.343 ± 0.033	0.352 ± 0.023	–	–	–
TDS_{lv}, cm	0.702 ± 0.024	0.718 ± 0.031	0.915 ± 0.032	–	30.3[b]	27.5[b]
TSS_{lv}, cm	0.436 ± 0.019	0.525 ± 0.023	0.778 ± 0.029	20.4[a]	78.4[b]	48.2[b]
T_{IVS}, d, cm	0.165 ± 0.005	0.128 ± 0.009	0.113 ± 0.015	–22.7[a]	–31.5[b]	–
T_{pw}, d, cm	0.168 ± 0.006	0.153 ± 0.005	0.157 ± 0.008	–	–	–
SF, %	37.85 ± 1.05	26.98 ± 0.39	14.58 ± 1.02	–28.7[b]	–1.5[b]	–45.9[b]
TDV_{lv}, mL	0.808 ± 0.068	0.850 ± 0.086	1.617 ± 0.156	–	100.1[b]	90.2[b]
TSV_{lv}, mL	0.215 ± 0.027	0.350 ± 0.050	1.067 ± 0.111	62.8[a]	396.3[b]	204.9[a]
SV, mL	0.569 ± 0.052	0.500 ± 0.071	0.583 ± 0.070	–	–	–
HR, beats/min	378.3 ± 11.1	364.0 ± 4.8	393.2 ± 7.5	–	–	–
EF, %	73.52 ± 1.31	58,48 ± 0.69	34.95 ± 2.12	–20.5[b]	–52.5[b]	–40.2[b]

([a]) Difference from control $p < 0.01$, ([b]) difference from control $p < 0.005$.

weight of the heart in rats in pathology did not change, its relative weight as compared with control and sham-operated animals increased by 15.1 and 24.1%, respectively. The relative LV weight in rats with CHF was higher than in control and sham-operated animals by 25 and 40.6%, respectively (Table 1). This is likely because the body mass of rats with pathology was somewhat lower than in control. The scar tissue volume in the LV 6 months after coronary occlusion fluctuated from 17.60 to 25.21% and amounted, on average, to 21.47% of the LV volume.

Damage to the myocardium leads to progressing cardiomegaly and CHF, which indicates ischemical cardiomyopathy with poor prognosis (Mareev et al., 2013). Chronic cardiac stress leads to progressing myocardial hypertrophy, during which the capabilities of the coronary circulation bed become insufficient for adequate perfusion of the myocardial mass. The steady structural ventricular dilation represents the final result of remodeling of myocardium (Nechesova et al., 2008; Bilsen et al., 2009). Current ideas suggest that the heart remodeling is considered as the general pathogenic process in patients with CHF of varying etiology. The final result of the processes occurring at all levels of the heart's structural organization is a change in its size, shape, and functional capabilities (Gaasch and Zile, 2011). At present, to assess the functionality of the heart, the EchoCG method is usually used, which is based on recording ultrasound waves that have been reflected from the surfaces of heart structures with different densities. The main advantage of this method consists in the fact that the EchoCG method is noninvasive (Gopal et al., 1995; Geyer et al., 2010).

Ultrasonic study of the heart has shown that changes occur in the overwhelming majority (12 out of 14) parameters of the structure and function of the LV of rat heart for 6 months (Table 2). The main, and the most significant, structural changes of the rat LV in CHF were an increase of its systolic and diastolic diameters and even stronger increase of the volume of cavities of this part of the heart (Table 2). TSS and

Table 3. Rate of oxygen consumption and carbon dioxide emission, as well as respiratory coefficient, of various rat experimental groups

Groups of rats	V_{O_2}, mL/kg/min	V_{CO_2}, mL/kg/min	Q
C	17.12 ± 0.92	12.87 ± 0.82	0.75 ± 0.04
SO	19.72 ± 1.04^{a}	14.80 ± 0.89^{b}	0.75 ± 0.01
CHF	$21.79 \pm 1.25^{a, c}$	$18.46 \pm 0.93^{a, e}$	$0.85 \pm 0.05^{a, d}$

VO_2 and VCO_2 are the rate of oxygen consumption and carbon dioxide emission, respectively; Q is the respiratory coefficient. Significance of differences: (^{a}) $p < 0.001$ from C, (^{b}) $p < 0.005$ from C, (^{c}) $p < 0.05$ from SO, (^{d}) $p < 0.01$ from SO, and (^{e}) $p < 0.001$ from SO.

TDS of the LV in rats with CHF increased by 78 and 30%, respectively ($p < 0.001$). The increase of the LV cavity volume in the systole and diastole was even more pronounced—396 and 100%, respectively ($p < 0.001$). Extension of the LV cavity was accompanied by thinning of IVS. The thickness of IVS in rats with CHF as compared with control animals decreased by 31.5% ($p < 0.005$).

The dilatation of the ventricle and hypertrophy of myocardium observed after MI are considered to be temporary compensatory responses to the LV dysfunction appearing as a result of damage to the myocardium (Urbanek et al., 2010; Gaasch and Zile, 2011). Extension of the viable myocardium and dilation of the LV cavity is aimed at maintaining of the pumping function under conditions of a decrease of the mass of the contracting myocardium. However, with damage to more than 20% of the myocardium, these compensatory processes turn out to be insufficient. Further increase of the LV cavity can restore systolic volume by compensating thereby for the decrease of ejection fraction; however, such dilation leads to an increase of systolic and diastolic myocardial stress, which, in turn, stimulates further dilation of the LV cavity. When the majority of the contracting myocardium dies, the vicious circle is closed and dilation aimed at maintenance of the LV pumping function will lead only to its further dilation. All this eventually ends in patient death, with this amounting in CHF to 30–40% of cases 1 year after infarction and to 50–60% in the 5 following years (Berger et al., 2004; Neubauer, 2007; Nechesova et al., 2008; Mareev et al., 2010, 2013).

In the experiment that was carried out, the structural LV changes in the course of its remodeling were accompanied by a significant worsening of its function. SF in CHF decreased by 62.8%, while in EF it decreased by 52.5%, relative to the corresponding parameters in control rats (Table 2). An increase of the LV in CHF promotes maintenance of its systolic volume (SV) against the background of a decrease of EF within the standard limits. It is thought that remodeling of the myocardium, including a change of shape and an increase in the volume of heart chambers, represents an adaptive reaction aimed at maintenance of cardiac output (CO) (Urbanek et al., 2010; Gaasch and Zile, 2011). Indeed, SV, HR, and CO in the group of rats with CHF were preserved at the level of control: SV was 0.583 and 0.569 mL, HR was 356 and 378 beats/min, and CO was 207 and 215 mL, respectively (Table 2). The sizes of aorta in control animals and in animals with CHF did not differ—0.39 ± 0.04 and 0.41 ± 0.04 cm, respectively. Nevertheless, the increased LV cavity in CHF promotes retention of SV and CO at the level of control values.

Determination of the EchoCG parameters in sham-operated rats revealed structural–functional LV changes that were similar to those in experimental rats, although the magnitude of these changes was smaller. In rats subjected 6 months earlier to thoracotomy and opening of the pericardium, there was an increase, compared with the control values, of the LV systolic diameter and chamber volume (by 20.4 and 82.8%, respectively) and a decrease of SF and EF (by 28.7 and 20.5%, respectively), leading to severe disturbances of the LV function (Table 2).

Thereby, in rats, as a result of ligation of the left coronary artery, an MI develops that is similar in its histological and echocardiographical characteristics to human MI (Fishbein et al., 1978). The MI and subsequent heart remodeling lead not only to severe disturbances of its structure and function, but also to a change in the physiology and metabolism of the organism as a whole (Bilsen et al., 2009; Gaasch and Zile, 2011).

One of the first symptoms of chronic left ventricular failure is dyspnea. During dyspnea, patients breath more frequently, as if trying to fill their lungs with the maximum possible volume of oxygen. Tachypnea in CHF has also been shown in rats (Hacker et al., 2006). The volume of the consumed oxygen allows accurate determination of the cardiovascular and pulmonary reserves and is very useful for prognostic evaluation of the state of the organism in CHF. The precise mechanism of excessive gas exchange in CHF is not quite clear. An increase of activity of the sympathetic and renin–angiotensin systems, elevation of efferent muscular nervous activity, an increase in the physiologically dead pulmonary space, and an earlier than normal development of metabolic acidosis, as well as an increase in heart size, are usually cited as causes of increased respiration rate in CHF (Sin and Man, 2003; Berger et al., 2004; Okonko et al., 2008). Patients with severe heart failure even in a state of complete rest are in a state of constant oxygen insuffi-

ciency, as the hindered functioning of the respiratory musculature and heart leads to constant accumulation of underoxidized products in blood (Lang, 1958; Friedman et al., 1976).

In the present work, oxygen consumption by rats was measured without any physical load, in a calm, low-motility state.

Measurement of gas exchange in various rat groups showed that, compared with control, the oxygen consumption in sham-operated animals increased by 15.2%, whereas in rats with CHF it increased by 27.3% (Table 2). CO_2 production in groups of sham-operated rats and in rats with CHF rose by 15.0 and 43.4%, respectively. The respiratory coefficient that reflects the character of substrates that have oxidized in the organism did not change in the sham-operated animals compared with control, but in rats with CHF it increased, attaining 0.85.

A lack of energy plays the chief role in development of heart failure (Neubauer, 2007). It has been shown that disturbances of energy metabolism in the myocardium appear very early in the postinfarction period and a decrease of energy reserves in the myocardium correlates directly with the parameters of disturbance of LV systolic and diastolic functions (Sin and Man, 2003). The rat heart contracts daily approximately 550 thousand times, pumping a huge volume of blood, the viscosity of which is 4.4–4.8 times higher than that of water. Naturally, such a large amount of work performed by the heart needs huge expenditures of energy.

A very large number of different biochemical pathways are involved in the production, transfer, and use of chemical energy in cardiomyocytes that provide maintenance of their viability and functioning. At present, there is an increasing amount of evidence obtained on the basis of clinical and experimental studies that heart failure is accompanied by significant disturbances of energy metabolism in the myocardium (Ingwall and Shen, 1999). The changes in the metabolism of the myocardium in CHF represent an important part of the total process of the postinfarction remodeling that often is called "biochemical remodeling." The chief mechanism providing synthesis of ATP in cardiomyocytes is the oxidative phosphorylation that occurs in mitochondria. This process is maintained through the production of reductive equivalents (i.e., of NAD-H) mainly via the cycle of tricarbonic acids and by controlled combustion of such substrates as free fatty acids and carbohydrates (glucose, lactate, pyruvate) (Stanley et al., 2005).

The function of the heart greatly depends on the rate of synthesis of ATP, which is formed mainly by oxidative phosphorylation in mitochondria and to a much lesser degree in the course of glycolysis. The majority of the energy (about 70%) that is expended by the myocardium for muscle contraction is formed from free fatty acids (Bilsen et al., 2009). It has been shown that, in CHF, there occur significant shifts in the energy metabolism of cardiomyocytes, which include disturbance of the functions of mitochondria and a decrease of the rate of oxidation of fatty acids. Meanwhile, the decrease in the rate of oxidation of fatty acids is partly compensated for by an increased use of carbohydrates (Bilsen et al., 2009). It is known that the value of the ratio V_{CO_2}/V_{O_2} (respiratory coefficient Q) depends on the composition of oxidizable substrates. When using lipids as a substrate, the Q value is about 0.7, while upon oxidàtion of carbohydrates it is 1.0. In correspondence with the results presented in Table 2, the Q value in the group of control rats amounts to 0.75. In spite of the increase in gas exchange in sham-operated rats, the Q value in this group of animals did not differ from that of control. The obtained data allow the conclusion to be drawn that control and sham-operated animals predominantly use lipids as oxidizable substrates. In the group of rats with CHF, the Q value increased to 0.85, which indicates a significant increase in the contribution of carbohydrates as energy substrates for functioning of the ischemic myocardium.

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